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Invited article

Cerebral complications of diabetes: clinical findings and pathogenetic mechanisms

Geert-Jan Biessels

Department of Neurology, University Hospital Utrecht; Department of Medical Pharmacology, Rudolf Magnus Institute for Neurosciences, PO Box 85500, 3508 GA Utrecht, The Netherlands

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Abstract

This review describes the cerebral complications of diabetes mellitus from a neuropsychological, neurophysiological and neuroradiological perspective. In addition, possible pathogenetic mechanisms are discussed. Neuropsychological studies of diabetic patients generally report modest deficits in learning and memory and information processing. Notably, in elderly diabetic patients cognitive deficits may be more prominent. Recent epidemiological studies show that in the elderly diabetes is associated with an increased risk for dementia. Neurophysiological studies show increased latencies of evoked potentials and event-related potentials. Neuroradiological findings are enhanced peripheral and central cerebral atrophy, as well as focal lesions.

The pathophysiology of the effects of diabetes on the brain has not been fully elucidated. The putative involvement of cerebral metabolic and microvascular disturbances, similar to those implicated in the pathogenesis of peripheral diabetic neuropathy, is discussed. In addition, the role of repeated hypoglycaemic episodes, cerebrovascular disease and hypertension is addressed. Finally, the potential differential effects of insulin dependent and non-insulin dependent diabetes on the brain are discussed, as well as possible links with brain ageing.

Keywords: Diabetes mellitus; Brain; Cognitive function; Ageing; Evoked potentials; Magnetic resonance imaging

Peripheral neuropathy is a well-known complication of diabetes mellitus [1,2]. In recent years evidence is emerging that diabetes also affects the central nervous system [3–5]. Both acute and chronic metabolic and vascular disturbances can impair the functional and structural integrity of the brain in diabetic patients. For example, diabetes increases the risk for stroke [6,7] and stroke outcome is worse in diabetic patients [8]. In addition, hyper- and hypoglycaemic episodes may result in acute cerebral dysfunction [9–11]. The consequences of these acute insults to the brain are well recognised and have been reviewed previously [8,11,12]. The present paper will focus on functional and structural cerebral alterations that develop more insidiously and tend to be more subtle. Recent neuropsychological, neurophysiological, and neuroradiological studies into the nature and the magnitude of the long-term

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effects of diabetes on the brain will be reviewed and possible pathogenetic mechanisms will be discussed.

Cerebral manifestations of diabetes

Cognitive function

Neuropsychological studies in diabetic patients have reported variable performance deficits on a wide range of cognitive tests. Problems with learning and memory, problem solving and mental and motor speed have been noted [13–21]. The nature and severity of cognitive deficits in diabetic patients appears to be dependent on age and possibly also on the type of diabetes (insulin dependent diabetes (IDDM) versus non-insulin dependent diabetes mellitus (NIDDM)).

Cognitive function in children with IDDM

In diabetic children age at diabetes onset and hypoglycaemic episodes appear to be the prime determinants of cognitive changes; children and adolescents who develop diabetes before 5 years of age [22,23] and children who frequently experience hypoglycaemic episodes [23–25] are more likely to express cognitive deficits. Visual and spatial abilities may even be affected by asymptomatic recurrent hypoglycaemia [24]. Disease duration and poor glycaemic control, as determined by HbA1 values, may be additional factors influencing cognitive function in diabetic children [22,26].

Cognitive function in adult IDDM patients

In adult IDDM patients small but detectable reductions in mental efficiency have been reported repeatedly [22]. Severe deficits occur only in few patients [27]. The pattern of impairment across different cognitive tasks tends to vary among studies [18]. This variation might be due to the relatively subtle nature of the cognitive deficits, as well as the heterogeneity of study populations. In addition, exposures to different risk factors such as frequent hypoglycaemic episodes, on the one hand, and chronic hyperglycaemia, on the other, may vary between patients.

Glycaemic control plays a dual role in the prevention of cerebral complications in adult IDDM patients. On the one hand poor glycaemic control, as reflected in increased HbA1 values, is associated with cognitive dysfunction [22,28]. Moreover, the development of other complications associated with poor glycaemic control, such as peripheral neuropathy, is associated with cognitive dysfunction [16]. On the other hand, intensive treatment increases the frequency of hypoglycaemic episodes [29,30], and may thus adversely affect the brain. In adult IDDM patients, the frequency of severe hypoglycaemic episodes has been shown to be inversely correlated with performance in cognitive tests [19,22,31–34]. It should be noted, however, that such a correlation has not been demonstrated invariably [17,29,35] and that the relation between repeated hypoglycaemic episodes and cognitive dysfunction remains subject to ongoing debate [36].

Cognitive function in NIDDM patients

Compared to IDDM, neuropsychological studies in NIDDM patients have provided more consistent results (Review [20,21]). In NIDDM patients moderate degrees of cognitive impairment have been reported, particularly in tasks involving verbal memory or complex information processing. Tasks that tap basic attentional processes, motor reaction time and immediate memory appear to be unaffected [20,21]. Although the exact impact on daily functioning remains unclear, the fact that differences between NIDDM patients and age-matched controls can be detected with relatively crude tests such as the mini mental state examination [37–40], suggests that the deficits are not insignificant.

Risk factors for cognitive dysfunction in NIDDM are increased HbA1 and fasting plasma glucose levels [41,42], elevated serum triglyceride levels [43], and the presence of peripheral neuropathy [41]. Since severe hypoglycaemic episodes are relatively uncommon in NIDDM patients [44,45], they do not appear to be a prime determinant of cognitive dysfunction in NIDDM.

Diabetes, hyperinsulinaemia and impaired glucose tolerance in the elderly

The prevailing view of the studies that have been discussed thus far is that cognitive functions can be impaired in diabetic patients, in particular those with NIDDM, but that the impact of these impairments on

day-to-day functioning appears to be limited. Although this conclusion may be valid for relatively young (age < 70 years) patients, it does not appear to hold true for the elderly. Recent epidemiological studies in elderly subjects have demonstrated an association between diabetes and dementia [46,47]. This association was evident for Alzheimer's disease (relative risk in diabetic patients ~1.5 [46,47]) as well as for vascular dementia (relative risk in diabetic patients ~2 [46]). These findings are in line with previous studies in elderly diabetic patients which show relatively marked deficits in cognitive functions compared to age matched controls [38–40,48–50]. The reasons why the effects of diabetes on the brain appear to be more prominent in the elderly are unclear. Importantly, cognitive functions in the elderly may be impaired in subjects with newly diagnosed diabetes [38], as well as in subjects with impaired glucose tolerance [38,51] and/or hyperinsulinaemia [38,51–53]. These observations indicate that the effects of diabetes on the brain in the elderly may be related to an increased vulnerability of the ageing brain to the diabetic condition rather than to a prolonged exposure to diabetes. Although at present there is insufficient evidence to support a causal relationship between alterations in glucose metabolism and cognitive dysfunction in the elderly, recent studies implicating impaired glucose handling in the pathophysiology of Alzheimer's disease [54,55] stress the necessity of further investigations into the relation between glucose, insulin and the brain.

The question arises whether cognitive impairments in diabetic patients may reflect a central equivalent of peripheral diabetic neuropathy. The next section of this review will describe neurophysiological and neuroradiological evidence for the existence of such a 'central neuropathy', or encephalopathy. It should be considered, however, that in addition to such an encephalopathy other factors might influence cognitive function in diabetic patients. For example, the prevalence of psychiatric disorders, in particular depressive and anxiety disorders, is increased in both IDDM and NIDDM [56,57]. This increased prevalence of depression in diabetes can result from an inability to cope with the stresses associated with diabetes, but alterations in monoaminergic function in the brain that are known to be associated with diabetes could also be involved [57–59].

Electrophysiological abnormalities

Evoked potentials

Evoked potentials are the electrophysiological manifestations of the brain's response to an external stimulus, such as a flash of light or a sound click. Measurement of the latency of evoked potentials of different modalities, including visual evoked potentials (VEPs), brainstem auditory evoked potentials (BAEPs), and somatosensory evoked potentials (SSEPs), have been widely used to examine the functional integrity of the central nervous system in diabetic patients [60].

In the BAEP five waves can be distinguished, designated wave I through V. Wave I, III and V are considered to reflect activity in the acoustic nerve, the pons and the midbrain, respectively [61]. In both IDDM and NIDDM patients the latency of wave I [62,63], as well as the interpeak latencies I–III and III–V, were increased [63–66]. The latency of the VEP P100 wave, which is thought to be generated in the visual cortex [67], was increased both in IDDM and in NIDDM patients [62,68–70]. P100 latencies correlated positively with the duration of diabetes and HbA1 levels [71,72] and could be improved by intensive insulin treatment [70].

Studies on SSEPs in diabetic patients have provided more variable results. Increased latencies of the central components of the SSEP have been reported [73], although most studies have only found significant conduction delays in peripheral components of the somatosensory pathways [66,74,75].

Event-related potentials

In addition to evoked potentials, the latencies of event-related potentials, such as the P300 wave are increased in both IDDM and NIDDM patients [13,76–78]. The P300 wave is a late cortical neurophysiological event associated with cognitive and mnemonic functions [79,80]. It is considered to reflect neuronal events underlying information processing and is strongly associated with attention and short-term memory [79,80]. The increased P300 latency in diabetic patients may reflect impairment of

higher brain functions, thus providing a link between electrophysiological and cognitive impairments.

Neuroradiological changes

Several studies have identified diabetes as a risk factor for the development of cerebral atrophy and focal white matter lesions (e.g. [81–83]). These observations have been substantiated in studies that specifically compared IDDM and NIDDM patients to age-matched controls. Cerebral atrophy, diagnosed on the basis of widened sulci and/or enlarged lateral ventricles, was more prevalent in diabetic patients [84–86]. In addition, focal lesions were observed in 69% of a group of IDDM patients, whereas comparable lesions were observed in only 12% of an age-matched control group [83]. It has been suggested that the radiological appearance of the brain in diabetic subjects mimics that of normal ageing, but appears to develop at a younger age than in non-diabetic subjects [85].

Pathogenetic mechanisms

The aforementioned studies demonstrate that diabetes can impair cerebral function and structure. Several pathogenetic mechanisms could be involved. Firstly, factors that are also implicated in the pathogenesis of peripheral diabetic neuropathy could play a role. Secondly, as the neuropsychological and neuroradiological alterations in diabetes mimic those observed in the ageing brain [21,85], and as elderly individuals appear to be more susceptible to the effects of diabetes on the brain than younger subjects, it may be suggested that diabetes interacts with, or accelerates, the ageing process of the brain. Thirdly, risk factors for cerebrovascular events such as hypertension and atherosclerosis may be involved [87–89]. Finally, repeated hypoglycaemic episodes could play a role, in particular in IDDM [22,36].

The next part of this review focuses the aforementioned pathogenetic mechanisms. Studies into the pathogenesis are mostly based on animal models, in particular the streptozotocin (STZ)-induced diabetic rat and the BB/Wor rat. STZ destroys pancreatic β-cells relatively selectively, leading to insulin deficiency and hyperglycaemia [90]. In the BB/Wor rat diabetes develops spontaneously, secondary to an immune-mediated destruction of the β-cells [91]. These models of IDDM have been used extensively to examine the pathogenesis of peripheral neuropathy (Review [92]), but can also be used to study the effects of diabetes on the brain [93,94]. Thus far, few studies have employed animal models of NIDDM.

Links with the pathogenesis of diabetic neuropathy

The pathogenesis of peripheral diabetic neuropathy is multifactorial, involving metabolic changes [95], neurovascular dysfunction [96] and changes in trophic support [97]. Metabolic changes include an increased flux of glucose through the polyol pathway, leading to accumulation of sorbitol and fructose and depletion of myo-inositol [95]. Other metabolic changes are an enhanced non-enzymatic glycation of neural proteins [98] and an imbalance in the generation and scavenging of reactive oxygen species [99]. Vascular changes include reductions in nerve blood flow [100,101] leading to a decreased endoneurial oxygen tension [102]. Metabolic and vascular changes may be linked to reductions in peripheral nerve conduction velocity through reductions in Na^+/K^+-ATPase activity, leading to alterations in transmembrane ion gradients [103,104].

Like in the peripheral nervous system, increased glucose levels in the brain [105–107] lead to enhanced polyol pathway flux [108] and accumulation of sorbitol and fructose [109,110]. However, sorbitol and fructose levels appear to be lower than in peripheral nerves [109,110]. Remarkably, brain myo-inositol content is increased in diabetic rats [110], contrasting the myo-inositol decrease in peripheral nerves [95]. Enhanced non-enzymatic glycation of neuronal and non-neuronal proteins has also been demonstrated in the brain and spinal cord of diabetic rats [98,111,112], although the levels of glycation products in the central nervous system appear to be much lower than in peripheral nerves [98,113]. Also, increased concentrations of lipid peroxidation by-products, indicative of oxidative damage, have been demonstrated in the cerebral microvasculature and in brain tissue of diabetic rats [114–116]. Furthermore, the activity of superoxide dismutase and catalase, enzymes involved in the antioxidant defence of the brain, is decreased [116,117].

Functional and structural alterations in the cerebral microvasculature of diabetic animals include thickening of capillary basement membranes, decreased capillary density [118–120] and regional decreases in cerebral blood flow [121–123]. In diabetic patients thickening of cerebral capillary basement membranes [124,125] as well as regional decreases [126,127] and increases [128,129] in cerebral blood flow have been reported.

Links with the pathogenesis of brain ageing

Several processes that have been implicated in the pathogenesis of diabetic complications are also implicated in brain ageing, including oxidative stress, non-enzymatic protein glycosylation and ischaemia [130,131].

Increased oxidation of proteins and lipids has been demonstrated in the brains of ageing rodents [132,133] and humans [134]. Ageing is also associated with an accumulation of advanced glycosylation end products (AGEs) in various tissues, possibly as a result of lower protein turnover [130]. Interestingly, the formation of AGEs is associated with the increased production of reactive oxygen species [130,135], thus linking non-enzymatic glycosylation to increases in oxidative stress. Finally, brain capillaries may undergo progressive degeneration during ageing, caused by amyloid deposits, thickened basement membrane, and reduced vessel elasticity [136,137]. In the long term, capillary abnormalities may lead to increased capillary resistance, which in turn can affect cerebral blood flow. The adverse effects of oxidative stress, AGEs and ischaemia may be partially mediated by disturbance of neuronal calcium homeostasis [131,138]. Sustained alterations in neuronal calcium homeostasis are suggested to present a final common pathway in the development of the neuropathological changes associated with brain ageing [139,140]. Like ageing, diabetes is associated with impairment of neuronal calcium homeostasis [131,141].

Obviously, the relative contribution of ischaemia, oxidative stress, the formation of AGEs and disturbance of neuronal calcium homeostasis in brain ageing and the development of cerebral complications of diabetes differs. However, the similarities are apparent and may explain part of the increased susceptibility of elderly diabetic patients to the effects of diabetes on the brain.

Cerebrovascular alterations

Diabetes is associated with an increased prevalence of hypertension [142,143] and cerebrovascular disease [12,144]. Cerebrovascular disease increases the risk of stroke [145] and may lead to haemodynamic alterations [12]. These haemodynamic alterations are reflected in the aforementioned regional alterations in cerebral blood flow. In addition, cerebral vasoreactivity is impaired in diabetic patients [146–148]. Cerebral vasoreactivity, and accompanying changes in blood flow, are important compensatory mechanisms during conditions such as hypoglycaemia, hypotension, hypoxia and hypercapnia. Loss of these compensatory mechanisms may have detrimental effects on the brain.

Hypertension may play both an indirect and a direct role in the pathophysiology of cerebral complications of diabetes. Hypertension accelerates the development of cerebrovascular disease [149]. In addition, hypertension predisposes to cognitive impairment in both non-diabetic [53,150] and diabetic [151] elderly. The pathophysiology of the effects of persistent hypertension on the brain is only partially understood. However, in the context of this review it is important to note that hyperinsulinaemia appears to potentate the adverse effects of hypertension on the brain, even in non-diabetic subjects [53].

Effects of hypoglycaemia

Cognitive changes that accompany a single episode of hypoglycaemia are considered to be transient [17]. However, repeated episodes of hypoglycaemia may lead to cumulative damage to the brain, causing permanent cognitive impairment [32,33]. Selective neuronal damage during hypoglycaemia has been shown to result from over-activation of a subtype of excitatory amino acid receptor, the *N*-methyl-D-aspartate(NMDA)-receptor, which is one of the main excitatory amino acid receptors on cerebral neurones [152]. NMDA-receptor over-activation leads to pathologically enhanced levels of free intracellular calcium [153,154], in turn leading to loss of nuclear and mitochondrial function and activation of pro-

teases and other calcium dependent enzymes [154–156].

Conclusions

Long-term diabetes mellitus can lead to cerebral disorders. Manifestations of these disorders include cognitive dysfunction, electrophysiological abnormalities and structural changes. The effect on daily functioning is generally assumed to be limited. However, in elderly diabetic patients impaired performance can be detected with tests like the mini mental state examination [37–40,48], suggesting that the deficits are not trivial. Moreover, epidemiological studies indicate that elderly diabetic patients are at increased risk for developing dementia [46,47]. The notion that the effects of diabetes on the brain are most marked in the elderly and mimic the effects of ageing provide a challenge for the clinician: the effects of diabetes need to be distinguished from those of 'normal ageing' to avoid underestimation of the impact of the effects of diabetes on the brain.

Thus far fewer studies have addressed the reversal of cognitive deficits in diabetic patients. Preliminary studies show that cognitive functions may improve with glycaemic control in elderly NIDDM patients [157–159]. It should be considered, however, that the balance between the potential harmful effects of chronic hyperglycaemia on the one hand and of repeated hypoglycaemic episodes on the other is delicate. In addition to optimising glycaemic control, increasing insight into the pathogenesis and identifying risk factors for cerebral dysfunction in diabetes may lead to the development of additional preventive and interventional measures. One of the key questions that needs to be answered is why the effects of diabetes on the brain appear to be more pronounced in the elderly. There are several possible explanations. Firstly, the aging brain may be more sensitive to the effects of diabetes due to a reduced 'cognitive reserve capacity' as a result of the wear and tear of ageing. In favour of this explanation is the finding that young adult IDDM patients express neurophysiological and neuroradiological deficits which are qualitatively similar to those in NIDDM patients, but do not appear to express clinically significant cognitive deficits. Alternatively, the pathogenetic processes of ageing and diabetes may interact, as was discussed in the previous section of this review, leading to an accelerated cognitive decline in the elderly. Finally, differences in the pathophysiology of IDDM and NIDDM may provide an explanation for the differential functional deficits in different age groups, as NIDDM is by far the most common form of diabetes in the elderly, whereas IDDM is the most common form in the younger population. For example, given the clustering of hyperinsulinaemia/insulin resistance with dyslipidaemia and hypertension in NIDDM [160,161], support for this latter hypothesis could be provided by the observation that hyperinsulinaemia potentiates the adverse effects of hypertension on the brain [53,151]. Moreover, even in relatively young NIDDM patients the pattern of cognitive deficits appears to be more consistent than in IDDM [76,162]. Still, as yet it remains uncertain whether ageing itself or differences in the pathophysiology of IDDM and NIDDM are the main determinant in the enhanced effects of diabetes on the brain in the elderly. The elucidation of the complex interplay between IDDM, NIDDM and ageing will provide a key challenge for future studies into the effects of diabetes on the brain.

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